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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,667	02/28/2002	A. John Bramley	2001796-0008	7908

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,667	BRAMLEY ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-44,46,47 and 49* is/are pending in the application.

4a) Of the above claim(s) *45 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-44,46,47 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation in pat of 09/337,079, filed June 21, 1999, now abandoned, which claims benefit to provisional application 60/090,175 filed June 22, 1998.

Claims 32-49 are pending.

Election/Restrictions

Applicant's election of Group VII, claims 47 and 49 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 45 and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Claims 32-44 and 46 link inventions I-XI. It is noted again that upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction

requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 32-44, 46, 47 and 49 are currently under examination to the extent they encompass the elected invention of a non-human transgenic mammal comprising an altered non-mammalian lysostaphin gene.

Information Disclosure Statement

The information disclosure statement filed July 9, 2002, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

A copy of the US patents could be obtained and reviewed by the Examiner. However the only references considered were those provided with the present disclosure. An initialed and signed copy of the PTO 1449 filed is provided with the instant action.

In addition, it is noted that the information disclosure statement filed July 9, 2002, fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other

information submitted for consideration by the Office. Specifically, several abstracts and references are provided however they are not listed in the PTO-1449. The references have been placed in the application file, but the information referred to therein has not been considered.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/090,175, filed June 22, 1998 and PCT/US99/14073, filed June 22, 1999 (see Declaration filed June 22, 2002) A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a).

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the

application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Specification

The disclosure is objected to because of the following informalities: the first line of the specification indicates the priority data only to US application, 09/337,079, filed June 21, 1999,

however the declaration seems to indicate a claim of priority to the provisional application 60/090,667 (see declaration). The specification should be amended to reflect the correct claim for priority.

Appropriate correction is required.

Claims

Claims 32-44, 46, 47 and 49 are objected to because of the following informalities: the claims encompass embodiments which are broader than the elected invention. It is noted that many of the claims link the elected invention to other non-elected inventions, and that the there may be opportunity for the examination of the linking claims. However, no linking claim has been found allowable, therefore additional inventions/embodiments will not be examined. The claims should be amended to reflect the elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose somatic and germ cells contain a transgene, wherein said transgene comprises a mammary gland specific promoter; a mammary gland specific enhancer; a DNA sequence encoding a secretion signal

sequence functional in mammary gland secretory cells; and a DNA sequence encoding an active antimicrobial protein wherein the transgenic non-human mammal expresses the transgene in mammary secretory cells such that the active antimicrobial protein is detectable in milk produced by the transgenic non-human mammal, does not reasonably provide enablement for a transgenic non-human mammal comprising a transgene encoding any anti-microbial protein in any tissue and/or cell of said mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are drawn to a transgenic mammal which comprises a transgene encoding any anti-microbial protein (linking claims), more specifically the anti-microbial protein lysostaphin elected claims 47 and 49. Dependent claims recite specific transgene modifications such as eukaryotic start codon, Kozak consensus sequence, a lysostaphin gene which encodes a protein wherein two glycosylation sites are removed, and promoter and enhancer elements for expression in mammalian secretory cells (linking claims). It should be noted that the claims do not require that the transgene be expressed nor does it define what tissues express the transgene. The specification teaches a lysostaphin gene construct wherein the open reading frame for lysostaphin has been modified for transcription and translation in mammalian secretory cells. Further, the sequence which encodes lysostaphin has been modified wherein the two glycosylation sites have been deleted in order to avoid the expression of an inactive form of lysostaphin. Finally, the transgene construct is used to create a transgenic mouse which produces and secretes an active form of lysostaphin into the milk of lactating mice.

First, none of the claims require that the transgene be expressed or produced in any tissue. While the claims recited genetic elements, such as promoters and enhancers, which are known to function in the mammary gland, there is no functional language in the claim that supports this embodiment. The broadest claim (claim 32) and other more narrow dependent claims simply recite the genetic elements that were necessary to obtain the successful transgene expression of lysostaphin in the transgenic mouse provided in the specification. Further, when read in light of the specification the nature of the invention is transgenic non-human mammals which produce antimicrobial proteins in their mammary gland and secrete said protein in their milk. While the anti-microbial phenotype produced by transgene expression may be extended to

other tissues by expression of an anti-microbial transgene with tissue specific promoters driving expression in that tissue, at the time the invention was made, the production of transgenic animals was still unpredictable. In order to produce proteins in the proper amount to be useful the design of the transgene construct is of paramount importance. Wall *et al.* summarizes the state of the art of transgene construct in "Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61; last paragraph). With respect to transgene expression of milk proteins Houdebine says "the regulatory elements involved in the control of milk protein gene expression are still far from being known in detail. The gene constructs using these promoters are therefore still done empirically, leading to unpredictable success and failure" (page 274; second column first paragraph). Even though the level of skill in the art is high, specific guidance and direction is required to provide the nexus of a proposed transgene construct and the successful use in a transgenic animal. Houdebine states that the vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriates regulatory elements (pages 272-3; bridging paragraph) and that transgenic expression is heavily dependent on its site of integration in the host genome which is unpredictable (page 277; second paragraph). Further, the promoters and methods used are specific for the type of animal selected (page 272; second paragraph). Mullins *et al.* states "the integration of a transgene into alternative species may result in widely different phenotypic responses" (page 631; center of first paragraph). Specifically, with respect to the anti-microbial activity associated with lysostaphin, recombinant lysostaphin protein has been successfully used in mastitis therapy. For example, Oldham *et al.* report that recombinant lysostaphin has different stability in different media (summarized in

Table 2). Further, for a therapeutic effect multiple minimal doses would be desirable (page 4180; second column), however that repeated administration of foreign proteins to a host often causes problems due to immunological reactions (page 4181; second column). Daley *et al.* support this observation demonstrating that delivery of lysostaphin by repeated administration (Table 1) and oral administration (Table 2) causes specific serum antibody titers to lysostaphin. Therefore, in order to successfully produce a transgenic animal, expression of the transgene must be such that it does not induce an immune response yet still produces enough of the recombinant protein to elicit a useful phenotype. Without the specific guidance to overcome these problems, the unpredictability of promoter activity and transgene insertion in the genome, as discussed above, results in an burdensome amount of experimentation needed to practice the invention. Finally, the claims encompass many species of mammals and the broadest claims recite the production of any antimicrobial protein wherein the expression of the transgene and production of the encoded protein is not limited to production as a milk protein. However, the specification demonstrates only one transgene construct which functions in the mammary cells of a transgenic mouse, and further the specification fails to teach what to do with transgene expression of an anti-microbial protein if expressed in other tissues.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to practice the invention commensurate in scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claim is vague and unclear in what is being altered in the transgene. Any transgene can be considered altered because it is out context of its normal location in the genome and often under the control of a heterologous promoter. The metes and bounds of the claim are unclear to what is being altered. Further, the claim requires sequences for expression, however what sequences are necessary or sufficient are not adequately defined because what is considered sufficient is not clearly set forth in the nor the specification. It is unclear if the claims include promoter sequences that adequate for expression in one context but not another and how one would determine if the promoter meets the limitations of the claims.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claim appears to be redundant in indicating that the anti-staphylococcal is an anti-staphylococcal.

Conclusion

No lcaim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach